

Efficacy of Ketamine in Bipolar Depression: Systematic Review and Meta-analysis

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Objective: To consolidate the evidence from the literature to evaluate the role of ketamine in the treatment of bipolar depression.

Methods: Major databases, including MEDLINE, EMBASE, Cochrane, and Scopus, were searched through October 2014, for studies reporting the role of ketamine in the treatment of bipolar depression. Only randomized controlled trials were included in the meta-analysis. We calculated standardized mean differences (SMDs) with SE for each study included in the meta-analysis. A random effect model was used to calculate the pooled SMDs. Heterogeneity was assessed using the Cochran Q test and I² statistic.

Results: Of the 721 articles that were screened, 5 studies that enrolled a total of 125 subjects with bipolar depression (mean age, 44.6±4.3 y and 65.6% females) were included in the systematic review; 3 randomized controlled trials (69 subjects) were included in the meta-analysis. The meta-analysis showed significant improvement in depression among patients receiving a single dose of intravenous ketamine compared with those who received placebo (SMD=-1.01; 95% confidence interval, -1.37, -0.66; *P*<0.0001). The maximum improvement was observed 40 minutes after the ketamine infusion. No heterogeneity was observed between the studies (Cochran Q test *P*=0.38, I²=0%). The 2 studies that were excluded from the meta-analysis also showed significant improvement in depression after ketamine therapy. Individual studies also reported improvement in anhedonia and suicidal ideation after ketamine therapy. None of the subjects had serious side effects, and the side effects were similar between the ketamine and placebo groups.

Conclusions: This study suggests that ketamine is effective in treatment-resistant bipolar depression and may reduce suicidal ideation and anhedonia.

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KEY WORDS: ketamine, bipolar depression, anhedonia, suicidal ideation

Bipolar disorder is among the most severe psychiatric disorders.^{1,2} The lifetime prevalence of bipolar disorder is approximately 4% in the United States, with depressive symptoms dominating during the long-term course of the illness.^{3,4} A number of treatment options are available for bipolar depression; however, none of them reduces symptoms rapidly, which can lead to disruption and poor quality of life among patients with bipolar depression.^{5,6} The delayed antidepressant effect can cause considerable morbidity, including increased suicidal risk.^{7,8} Therefore, a therapeutic agent with rapid antidepressant action could decrease the suicidal rate, improve quality of life, and decrease the burden on mental health services. Ketamine is an anesthetic medication that acts as an antagonist of the N-methyl-D-aspartate receptor and targets glutamate, which is an excitatory amino acid

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A.K.P. has full access to data and takes responsibility for the integrity and accuracy of the data.

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neurotransmitter.⁹ Preclinical studies have demonstrated the antidepressant effects of ketamine,^{10–12} and these studies have been followed by clinical trials in humans. Ketamine is thought to improve depression mainly by acting on the glutamatergic system and, as a result, enhancing 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid throughout.^{12,13} Ketamine may also act as a partial agonist of dopamine D₂ receptors,^{14,15} and it may increase dopamine levels in the striatum.¹⁶ In humans, multiple randomized controlled trials (RCTs) have shown the beneficial role of a sub-anesthetic dose of ketamine in major depressive disorder (MDD) that is resistant to other medications and electroconvulsive therapy.^{17–19} Intravenous ketamine has been shown to have a rapid but transient antidepressant effect, with a peak effect within 24 hours, and the effect may last for several weeks in a few patients.⁹ Even though multiple studies have demonstrated the beneficial role of ketamine in MDD, evidence supporting the role of ketamine in the treatment of bipolar depression is limited. Therefore, the systematic review and meta-analysis described here were performed to summarize and appraise the totality of evidence in the literature about the efficacy of ketamine in bipolar depression, including in patients with both bipolar I and II disorder.

METHODS

Data Sources and Search Strategies

A comprehensive search was conducted from Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus, through October 2014. The search strategy was conducted by an experienced librarian using a combination of controlled vocabulary and keywords (ketamine AND depression OR depressive disorder OR bipolar disorder OR mood disorder OR affective disorder OR bipolar depression or antidepressant). References of potentially eligible articles were also reviewed to broaden the search for potentially eligible studies.

Study Selection

Pair of reviewers working independently identified studies of any design, including case series, that

enrolled subjects of any age with bipolar depression who were treated with ketamine and that reported primary outcome as change in depression after ketamine therapy. Studies were selected without imposing any restrictions based on language of publication. Any disagreement between the reviewers was resolved by consensus, and chance adjusted agreement for steps requiring judgment was assessed using kappa statistics.²⁰ Case reports were excluded from the systematic review. The study's eligibility criteria for the meta-analysis were: (1) RCTs, (2) subjects with bipolar depression enrolled, (3) reports of mean change in depression score between ketamine and placebo.

Data Collection and Quality Assessment

Data from the studies that were included were extracted by 2 reviewers using a standardized data extraction form. We extracted data for study characteristics (author, year, country, study design, sample size, demographic characteristics of study participants, inclusion and exclusion criteria, and conclusion), type of intervention, outcome measures, and follow-up.

We used Cochrane Collaboration's Risk of Bias Tool to assess the methodological quality of trials included in the meta-analysis.²¹ Risk of bias was assessed in duplicate by 2 reviewers for random sequence generation, allocation concealment, blinding of participants, caregivers, or study personnel who assessed outcomes, incomplete outcome data, selective reporting, and other biases including funding source and nature.

Statistical Analyses

Continuous variables were reported as mean \pm standard deviations (SDs), and categorical variables as frequency and proportions. Standardized mean difference (SMD) with 95% confidence interval was calculated for each study included in the meta-analysis. SMD was calculated as maximum difference in pre-post treatment mean changes between the patients with bipolar depression treated with ketamine versus those treated with placebo divided by the pooled SD of the measurement. SMD is used as a summary statistic in meta-analysis when the studies assess the same outcome

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but measure it in a variety of ways. We used the random Der-Simonian and Laird effects model as it accounts for between-study heterogeneity.²² Heterogeneity among the studies included in the meta-analysis was assessed using the I^2 statistic and the Cochran Q test.²³ A P -value <0.10 on the Cochran Q test suggests that heterogeneity is due to between-study factors rather than sampling errors.²³ All other P -values were considered statistically significant at $P<0.05$. Review Manager (RevMan) Version 5.2 (Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2011) was used to perform all statistical analysis.

RESULTS

Study Selection

Initial searches identified 721 abstracts. After preliminary screening of titles and abstracts, 710 articles were excluded because they did not meet the inclusion criteria. The selection process for articles is described in Figure 1. Eleven articles were selected for full-text review. After the full-text review, 5 studies met the inclusion criteria for systematic review,^{5,13,24–26} and only 3 studies met the criteria for the meta-analysis.^{5,13,24} The interobserver agreement during both phases of study selection was excellent (>0.95).

Characteristics of Included Studies

Five studies (3 RCTs, 1 open study, and 1 case series) enrolling 125 patients were included in the systematic review (Table 1). One study enrolled patients with both bipolar depression and MDD²⁵; however, only data from the patients with bipolar depression were included in this systematic review. All of the studies used intravenous ketamine except the study by Lara et al,²⁵ in which ketamine was administered sublingually. The 3 studies included in the meta-analysis were randomized, double-blind, placebo-controlled, crossover clinical trials.^{5,13,24} These 3 trials enrolled 69 patients with treatment-resistant bipolar depression who received ketamine (concomitant with lithium or valproate used within the specific range of therapeutic levels). The mean age of participants was 44.6 ± 4.3 years with 65.6% female. A detailed description of the inclusion and exclusion criteria and adverse events reported in these studies is presented in Table 2.

Quality Assessment

The quality assessment of the 3 RCTs that were included in the meta-analysis is shown in Table 3. All studies were of good quality with low risk of bias on 6 criteria with unclear risk of other bias.

FIGURE 1. Flow diagram for the selection of references.

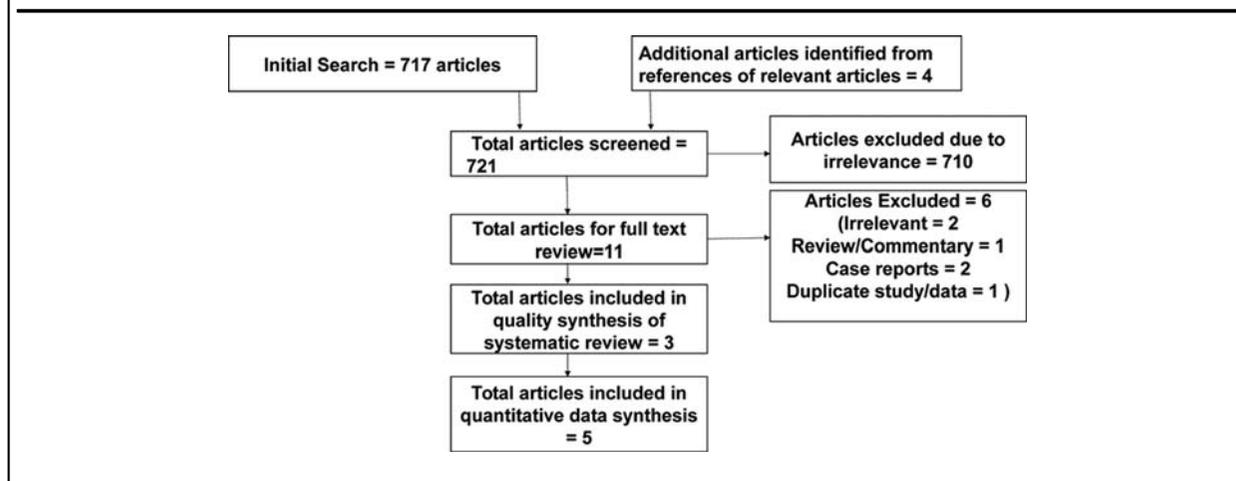


TABLE 1. Characteristics of the Studies Included in the Analysis

References, Country	Type of Study	Total Patients Females [n (%)]	Age (y) (Mean±SD)	Primary Outcome	Results/Conclusions
Lally et al, ²⁴ US	RCT*	36 21 (58.3)	46.7±11.1	Improvement in anhedonia and MADRS score	Ketamine rapidly reduced levels of anhedonia and depression, with effects lasting up to 14 d
Zarate et al, ¹³ US	RCT*	15 8 (53.3)	46.7±10.4	Change in MADRS	Single ketamine dose caused rapid and robust antidepressant response and rapidly reduced suicidal ideation
Diazgranados et al, ⁵ US	RCT*	18 12 (66.7)	47.9±13.1	Change in MADRS	Single intravenous dose of ketamine resulted in robust and rapid antidepressant effects
Lara et al, ²⁵ Brazil	Open case study	14 9 (64.3)	37.2±11.9	Change in mood level, cognition, and sleep	Clear remission of depression (reduction of ≥50% score on the Ham-D) in 8 subjects, moderate improvement in 5 subjects, and no response in 1 subject. Sublingual ketamine may have broad spectrum effects beyond antidepressant properties with good tolerability
Permoda-Osip et al, ²⁶ Poland	Open study	42 32 (76.2)	22-67 (range)	Reduction of ≥50% score on the Ham-D	Ham-D score at baseline 22.6±5.1; after 24 h, 15.6±7.4, and after 14 d, 11.8±7.8 Ketamine resulted in rapid antidepressant effect which was maintained for 2 wk with good clinical tolerance. Patients showing clinical improvement had higher frequency of alcohol addiction and family history of alcoholism

Only patients with bipolar depression were included in this systematic review. All studies except 1 administered a single dose of intravenous ketamine. In that study,²⁵ ketamine was given by sublingual route (10 mg from 100 mg/mL solution for 5 min with administration repeated every 2 to 3 d or weekly).

**Randomized controlled trial: double-blind, crossover, placebo-controlled.*

Ham-D indicates Hamilton Rating Scale for Depression; MADRS, Montgomery-Åsberg Depression Rating Scale.

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TABLE 2. Inclusion/Exclusion Criteria and Adverse Events (AEs)

<i>References</i>	<i>Inclusion Criteria</i>	<i>Exclusion Criteria</i>	<i>AEs</i>
Lally et al ²⁴	Subjects 18-65 y of age with treatment-refractory BD I or II without psychotic features currently experiencing MDE of at least 4 wk duration; MADRS score \geq 20 at screening; failed to respond to at least 1 adequate antidepressant trial before hospital admission	Pregnancy, nursing, serious suicidal ideation, comorbid substance abuse or dependence within past 3 mo, and previous use of or treatment with ketamine	Not reported
Zarate et al ¹³	Subjects 18-65 y of age with BD I or II without psychotic features currently experiencing MDE of at least 4 wk duration; MADRS score \geq 20 at screening and at the start of each infusion; failed to respond to at least 1 adequate antidepressant trial and a prospective open trial of a mood stabilizer while on the Mood Disorders Research Unit at the National Institute of Mental Health, Bethesda, MD; in good general health	Pregnancy, nursing, any serious unstable medical condition, comorbid substance abuse or dependence in 3 mo before enrollment, previous treatment with ketamine, or concomitant treatment with psychotropic medications other than lithium or valproate in 2 wk before randomization	No serious AEs. AEs during infusion in \geq 10% of subjects: feeling woozy or loopy, feeling lethargic or drowsy, cognitive impairment, fear or anxiety, nausea, dizziness, odd sensations, blurred vision, and headache, with no difference in AEs between ketamine and placebo groups. Headaches, drowsiness or sedation, early morning awakening, and difficulty falling asleep reported in 10% of both groups. Dry mouth, dizziness or faintness, difficulty falling asleep, and flatulence reported in ketamine group only; irritability and muscle, bone, or joint pain reported in placebo group only
Diazgranados et al ⁵	Inpatients 18-65 y of age with BD I or II without psychotic features experiencing MDE of at least 4 wk duration; MADRS score \geq 20 at screening and at start of each infusion; failed to respond to at least 1 adequate antidepressant trial and a prospective open trial of a mood stabilizer while on the Mood Disorders Research Unit at the National Institute of Mental Health, Bethesda, MD	Pregnancy, nursing, serious unstable medical disorder or condition, comorbid substance abuse or dependence in 3 mo before enrollment, clinically judged to be at serious risk of suicide, previous treatment with ketamine, or concomitant treatment with psychotropic medications other than lithium or valproate in 2 wk before randomization	No serious AEs. AEs during infusion in \geq 10% of subjects in both groups: feeling woozy or loopy, feeling lethargic or drowsy, cognitive impairment, fear or anxiety, nausea, dizziness, odd sensations, blurred vision, and headache. AEs in 10% of ketamine group only: dissociation; feeling strange, weird, or bizarre; dry mouth; tachycardia;

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TABLE 2. Inclusion/Exclusion Criteria and Adverse Events (AEs) (continued)

<i>References</i>	<i>Inclusion Criteria</i>	<i>Exclusion Criteria</i>	<i>AEs</i>
Lara et al ²⁵	Patients with bipolar depression experiencing a depressive episode with unsatisfactory response to at least 4 pharmacological treatments indicated for their disorder alone or in combination given for at least 4 wk at standard therapeutic doses	NA	and increased blood pressure. No significant difference between ketamine and placebo groups at 80 min after infusion or thereafter. Two patients reported mild agitation for a few hours. Mild light-headedness was common but transient, typically subsiding in <30 min and more pronounced or present only after first dose
Permoda-Osip et al ²⁶	NA	NA	NA

BD indicates bipolar disorder; MADRS, Montgomery-Åsberg Depression Rating Scale; MDE, major depressive episode; NA, not available; NIMH, National Institute of Mental Health.

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Depression scores were significantly improved in patients receiving a single dose of intravenous ketamine compared with those who received placebo (pooled SMD=-1.01; 95% confidence interval, -1.37, -0.66; $P<0.0001$). Figure 2 shows the statistically significant

pooled SMD, whereas SMD expresses the size of the intervention effect in each study relative to the variability observed in that study. Maximum effect was seen within 40 minutes of a single ketamine infusion and the effect lasted up to 14 days. No heterogeneity was observed between the studies (Cochran Q test $P=0.38$).

TABLE 3. Quality Assessment of the Clinical Trials Included in Meta-Analysis

<i>Quality Assessment Criteria</i>	<i>Lally et al²⁴</i>	<i>Zarate et al¹³</i>	<i>Diazgranados et al¹⁵</i>
Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence	Low risk	Low risk	Low risk
Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment	Low risk	Low risk	Low risk
Performance bias due to knowledge of the allocated interventions by subjects and personnel during the study	Low risk	Low risk	Low risk
Detection bias due to knowledge of the allocated interventions by outcome assessors	Low risk	Low risk	Low risk
Attrition bias due to amount, nature, or handling of incomplete outcome data	Low risk	Low risk	Low risk
Reporting bias due to selective outcome reporting	Low risk	Low risk	Low risk
Bias due to problems not covered elsewhere	Uncertain	Uncertain	Uncertain

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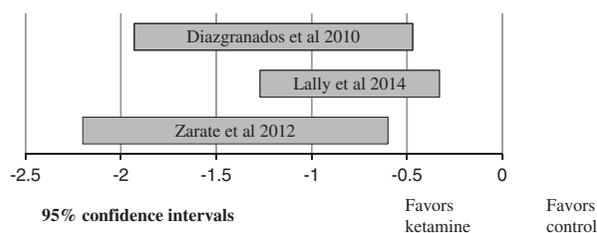
FIGURE 2. Meta-analysis: Ketamine's Efficacy in Bipolar Depression.

Study or Subgroup	Standard Mean Difference	SE	Weight (%)	Standard Mean Difference IV, Random, 95%CI
Diazgranados et al ⁵	-1.2	0.37	23.9	-1.20 (-1.93, -0.47)
Lally et al ²⁴	-0.8	0.24	56.7	-0.80 (-1.27, -0.33)
Zarate et al ¹³	-1.4	0.41	19.4	-1.40 (-2.20, -0.60)
Total			100	-1.01 (-1.37, -0.66)

Heterogeneity: $\tau^2=0.00$; $\chi^2=1.93$; $df=2$ ($P=0.38$); $I^2=0\%$.

Test for overall effect $Z=5.60$ ($P<0.00001$).

CI indicates confidence interval.



In addition to depression, ketamine also reduced anhedonia²⁴ and suicidal ideation.¹³ The 2 studies that were not included in the meta-analysis also showed a significant decrease in primary depression scores after treatment with ketamine. One study²⁵ enrolled subjects with both MDD and bipolar depression; however, we included only the 14 patients with bipolar depression in our analysis. After sublingual ketamine, 8 subjects showed clear remission of depression, 5 showed moderate improvement, whereas no response was seen in 1 subject. In addition to depression, ketamine also improved cognition and sleep in the majority of the patients. The other study that was not included in the meta-analysis²⁶ enrolled 42 subjects with bipolar depression and reported that the severity of depression on the Hamilton Rating Scale for Depression decreased significantly 24 hours after the administration of ketamine (from 22.6 ± 5.1 to 15.6 ± 7.4 points). Patients who showed clinical improvement had a significantly higher frequency of alcohol addiction and family histories of alcoholism.

Adverse Events

Three studies reported adverse events.^{5,13,25} No serious adverse events were reported in any of those studies. The adverse events that were reported were similar between the ketamine and control

groups in the 2 RCTs.^{5,13} A detailed description of the adverse events is presented in Table 2.

DISCUSSION

This systematic review suggests that ketamine can significantly reduce depression in patients with treatment-resistant bipolar depression. These studies enrolled patients with both bipolar I and bipolar II disorder; therefore, our results are generalizable to both subgroups. Our meta-analysis of the 3 RCTs that enrolled 69 patients showed a significant improvement in mean primary depression scores in the groups that received ketamine therapy compared with the control groups. Results from the 3 RCTs were homogenous. These results suggest that ketamine causes rapid and robust antidepressant response in patients with bipolar depression that may last up to 14 days. In addition to depression, ketamine also reduced levels of anhedonia independent of depressive symptoms, and this effect also lasted up to 14 days.²⁴ The anti-anhedonic effect of ketamine has been shown to be associated with increased glucose metabolism in the dorsal cingulate cortex and putamen, emphasizing the role of these brain regions in the neurobiology of the anti-anhedonic effect.²⁴ As anhedonia is prevalent in bipolar depression and no approved treatment for it exists, ketamine may play an important role in

treating anhedonia in addition to depression in patients with bipolar depression.

Our findings are consistent with a previous study that involved a limited number of patients with bipolar depression.²⁷ The safety and tolerability of ketamine was excellent in the studies we reviewed, and none of the patients in our systematic review showed serious adverse events. Mild to moderate adverse events were similar between the ketamine and control groups.

The major limitation of our systematic review and meta-analysis is the small number of studies included. Because of this limited number of studies, we were not able to assess for publication bias. Meta-analyses with <20 studies have a limited power to detect publication bias.²⁸ All of the studies we evaluated included patients with both bipolar I and bipolar II depression and reported combined outcome data for both groups. Therefore, it is difficult to interpret if the efficacy of ketamine in bipolar depression would differ in patients with bipolar I versus bipolar II disorder. Future studies should assess the efficacy of ketamine in bipolar I and II depression separately to quantify any difference in efficacy between the 2 groups.

This systematic review also had several strengths, including the exhaustive literature search strategy, the duplicate process used during the study selection and quality assessment to reduce measurement bias, and the use of a random effects model for analysis (to take into account the presence of between-study heterogeneity).

In conclusion, this systemic review and meta-analysis suggests that ketamine is effective in treatment-resistant bipolar depression. Future studies should focus on the long-term efficacy of repeated ketamine doses on treatment-resistant bipolar depression, suicidal ideation, and anhedonia.

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